IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AMICUS THERAPEUTICS US, LLC and AMICUS THERAPEUTICS, INC., *Plaintiffs*, v. TEVA PHARMACEUTICALS USA, INC., *et al.* *Defendants*.	C.A. No. 1:22-cv-01461-CJB CONSOLIDATED

DEFENDANTS, AUROBINDO PHARMA LTD. AND AUROBINDO PHARMA USA, INC.'S OPENING POST-TRIAL BRIEF IN SUPPORT OF INVALIDATING ASSERTED PATENTS

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Unless otherwise stated, the abbreviations below have the meanings ascribed to them in the right-hand column throughout the Defendants, Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc.'s Opening Post-Trial Brief in Support of Invalidating Asserted Patents.

ABBREVIATION	MEANING
'388 patent	U.S. Patent No. 11,633,388 (JTX-1)
'490 patent	U.S. Patent No. 12,042,490 (JTX-2)
'164 patent	U.S. Patent No. 11,833,164 (JTX-3)
'011 patent	U.S. Patent No. 9,000,011 (DTX-14)
α-Gal A	The enzyme α-galactosidase A
POSA	Persons of ordinary skill in the art
Tr.	Trial Transcript

Aurobindo Pharma Ltd. and Aurobindo Pharma USA, Inc. (collectively, "Aurobindo"), through their undersigned counsel, hereby respectfully submit Aurobindo's Opening Post-Trial Brief In Support of Invalidating Asserted Patents and in support thereof states as follows:

I. INTRODUCTION

Each of the patent claims Plaintiffs have asserted against Aurobindo to protect and further their $30,000/month/U.S. prescription patent stranglehold on the market for their migalastat product is directed to treating Fabry Disease, a rare genetic disease, with migalastat hydrochloride at a dose of 150 mg every other day.[1] *See* JTX-1-60, JTX-1-61 (claims 8 and 36); JTX-2-52 (claim 9); and JTX-3-89 (claims 23-27); *see also* Trial. Tr. Vol. I at 166:11-16; 168:4-13 (Mr. Keavany testifying regarding Galafold packaging and pricing). Viewed as such, as the asserted patents themselves acknowledge, the asserted claims describe only what was already fully known and practiced by researchers in the prior art and, in fact, had already been (a) previously protected by Plaintiffs in U.S. patent No. 9,000,011 ("'011 patent" or "DTX-14") and (b) approved as a Fabry treatment for Plaintiffs to market in Europe. *See* JTX-1-1 (citing '011 patent at "U.S. Patent Documents" and Galafold product descriptions dating back to May 30, 2016, at "Other Publications"); JTX-1-45 at 37:60-38:13 (describing "several studies" that "investigated using 150 mg migalastat hydrochloride every other day (QOD) in Fabry patients" and determined that dosing regimen to be effective); JTX-2-41 at 29:39-58 (same); JTX-2-3 at right column (citing Galafold product descriptions dating back to May 30, 2016); JTX-3-4 at right column (same); DTX-14 at claim 1; Tr. at Vol. I at 166:20-21; 215:17-217:3; 257:13-258:16; 260:17-263:21; *see also*, *e.g.* DTX-6-1, 6-2 ("Benjamin 2016") (describing migalastat as treating Fabry patients "with amenable mutations"); DTX-23-10 at Table 2 ("Wu") (disclosing administering 150 mg migalastat

[1] Plaintiffs have asserted U.S. Patent Nos. 11,633,388 ("'388 patent" or "JTX-1"); 12,042,490 ("'490 patent" or "JTX-2"); and 11,833,164 ("'164 patent" or "JTX-3").

hydrochloride to Fabry patients every other day); DTX-24-2 ("Germain 2012") (discussing the conduct and results of two clinical studies of 150 mg migalastat hydrochloride administered to Fabry patients every other day).

It was also well-known that only a limited percentage of Fabry patients could even possibly benefit from migalastat, and methods had been developed, including by Plaintiffs but also others, to try to identify mutations likely to be amenable to migalastat treatment. *See*, *e.g.*, Tr. Vol. I at 132:22-134:17 (Dr. Medin addressing JTX-13 and JTX-14 and noting the authors conducted their own HEK Assays using their own amenability criteria); JTX-1-35 at 17:17-35 (describing "previous screening methods" and expressly incorporating mutations determined to be amenable using methods described in U.S. patent No. 8,592,362 ("'362 patent")); JTX-2-35 at 17:28-53 (same); JTX-3-29 at 26:12-28 (same); DTX-14-1 at abstract ("Provided are in vitro and in vivo methods for determining whether a patient with Fabry Disease will respond to treatment with a specific pharmacological chaperone"); DTX-14-16 at 13:22-14:36 (discussing "Eligibility Determination Criteria" and describing *in vitro* and *in vivo* assays for determining eligibility/amenability for pharmacological chaperone therapy); DTX-6-2 (describing migalastat as an "investigational chaperone for patients with amenable mutations"); DTX-23-1 at abstract (describing a study of a "cell-based assay in cultured HEK-293 cells" that is "a useful aid in the identification of Fabry patients with AT100 [aka migalastat hydrochloride]-responsive mutant forms"); DTX-24-2 (describing migalastat hydrochloride as "a low molecular weight iminosugar that is orally bioavailable and that . . . target[s] α-Gal A mutants that maintain catalytic competence").

Stripped down to eliminate what had come before, the asserted claims stand out only in one respect: they identify specific Fabry mutations, including, with respect to the '388 and '490

patents, mutations the patentees determined to be amenable using their own amenability assay according to their own amenability criteria. The asserted claims do not actually claim Plaintiffs' amenability assay, the so-called GLP-HEK Assay, and there is no step in any of the claimed methods requiring performance of the assay or even consulting the assay results. Instead, the claims do no more than point either to specific Fabry mutations without regard to their alleged amenability, as with the '164 patent, or point to specific Fabry mutations that met the patentees' self-selected amenability criteria, which have shifted over time. (*See* Tr. Vol. II at 59:16-60:4 (Dr. Benjamin reading her own publication's endorsement of the precursor to the GLP-HEK Assay); Tr. Vol. II at 35:23-42:22 (Dr. Benjamin discussing the Wu prior art reference (DTX-23) and noting that the results discussed therein were not definitive; discussing further assay development).

As new mutations evolve or, as with the '164 patent, are hypothecated, and as additional mutations are identified as migalastat amenable, new patent claims are filed by Plaintiffs and their Galafold product's list of amenable mutations grows. (*See* Tr. Vol. II at 55:15-57:16 (Dr. Benjamin testifying regarding label and patent expansion.) In this way, Plaintiffs aim to secure patent protection in perpetuity as new Fabry mutations evolve or are hypothecated in a lab and meet Plaintiffs' amenability criteria. Neither 35 U.S.C. §§ 101 nor 103 permit them to do so.

Aurobindo contends that, at trial and as further detailed herein, Aurobindo demonstrated by clear and convincing evidence that the asserted claims are invalid as being (a) directed to unpatentable subject matter under § 101 and (b) obvious under § 103. Clearly controlling precedent applying § 101 prevents Plaintiffs from essentially re-patenting their previously patented method of treatment by coupling it with naturally occurring mutations even if the mutations were not previously known to be migalastat-amenable. *See*, *e.g.*, *Mayo Collaborative Svcs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012); *see also Athena Diagnostics, Inc. v. Mayo*

Collaborative Svcs., LLC, 915 F.3d 743 (Fed. Cir. 2019); *INO Therapeutics LLC v. Praxair Distrib. Inc.*, 782 Fed. App'x 1001, 1003 (Fed. Cir. 2019). And, persons of ordinary skill in the art before the priority dates of the asserted patents, which are not disputed,[2] would have been motivated to combine Plaintiffs' own prior art publications with at least a reasonable likelihood of successfully arriving at the claimed methods to treat any missense mutation, which are reasonably likely to be amenable to migalastat.

II. ARGUMENT

A. The Asserted Claims are Invalid Under 35 U.S.C. § 101.

The § 101 analysis first requires the Court to determine whether the asserted claims are directed to unpatentable subject matter. *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 573 U.S. 208, 217-18 (2014) (describing the two-step analysis). Aurobindo respectfully submits that, based on the plain language of the asserted claims themselves as well as the information provided in the asserted patent specifications, the asserted claims effectively seek to protect a well-known dosing regimen directed to any Fabry mutation ever determined to be amenable to migalastat according to Plaintiffs' GLP-HEK Assay and the standards Plaintiffs themselves set for assessing amenability.

Once it is determined that the claims are directed to unpatentable subject matter, the § 101 analysis requires the Court to determine whether the claimed inventions do anything to convert the unpatentable subject matter into a patentable invention. *Id.* In this case, they do not. With or without the amenability assessment factoring in, the asserted claims describe dosing methods that do not change depending upon the specific mutation or its amenability to migalastat. And the amenability assessment, which cannot provide the inventive step in any case, says only that the

[2] The agreed upon priority date for the '388 and '490 patent claims is May 30, 2017; the agreed upon priority date for the '164 patent is August 7, 2019.

mutations claimed in the '388 and '490 patents met the patentees' chosen criteria, which is another way of saying it tells practitioners nothing. Thus, even if the amenability determinations are considered, they do not tell practitioners how, when or even to whom to administer migalastat safely and effectively. Therefore, the asserted claims fail to meet the patentability standards of § 101.

i. The Asserted Claims Are Directed to Unpatentable Subject Matter.

The asserted claims are not all related. Nor are they all structured or phrased identically. Yet, at their narrowest they all claim (a) a method for treating Fabry Disease to a "patient in need thereof," (b) the method comprising administering to the patient 150 mg of migalastat hydrochloride (the equivalent of 123 mg of migalastat free base) (*see*, *e.g.*, Tr. Vol. I at 86:2-87:12) every other day and (c) wherein the Fabry patient has the or one among several (naturally occurring) Fabry mutations specifically identified in the respective claims. (*See* Tr. Vol. I at 230:24-231:2.) The '388 and '490 patent claims go further and expressly incorporate the patentees' chosen amenability criteria, which reflects their measurement of migalastat's natural effect on the target mutation.[3] (*See* Tr. Vol. I at 61:5-63:12 (Dr. Medin describing HEK Assays); Tr. Vol. II at 34:16-19 (Dr. Benjamin describing HEK Assay development as directed toward "measur[ing] the response of the mutant form and its response to migalastat"), 35:7-15 (describing the R&D HEK-Assay as assessing the mutation's response to migalastat).) Moreover, the asserted patents all cite to prior art descriptions of the dosing regimen, and the '388 and '490 patents detail

[3] The '388 and '490 patents use the phrase "HEK assay amenable mutation" to describe the specified mutations. The parties agreed "HEK assay amenable mutation" should be construed to mean "a mutant form of α-galactosidase A ("α-Gal A") showing a relative increase of ≥ 1.2-fold over baseline and an absolute increase of ≥ 3.0% wild-type α-Gal A activity in the presence of 10 μmol/1 migalastat determined using the Good Laboratory Practice ("GLP") HEK assay." In other words, "HEK assay amenable mutation" is expressly defined by reference to migalastat's natural effect on the relevant mutation. The '164 patent refers to each of the mutations identified in the asserted claims as "an α-galactosidase A mutation" without regard to migalastat amenability.

prior art descriptions as well. JTX-1-1 (citing '011 patent at "U.S. Patent Documents" and Galafold product descriptions dating back to May 30, 2016, at "Other Publications"); JTX-1-45 at 37:60-38:13 (describing "several studies" that "investigated using 150 mg migalastat hydrochloride every other day (QOD) in Fabry patients" and determined that dosing regimen to be effective); JTX-2-41 at 29:39-58 (same); JTX-2-3 at right column (citing Galafold product descriptions dating back to May 30, 2016).

These factors establish that the asserted claims are directed to the natural laws of Fabry mutation development and, with respect to the '388 and '490 patents, migalastat amenability and must, therefore, be evaluated under the second step of the *Alice* framework. *See INO Therapeutics LLC*, 782 Fed. App'x at 1005 (holding that method of treatment claims describing administration of a prior art therapy was directed to a natural law when the method otherwise allows "the body's natural processes . . . to take place"); *see also Mayo Collaborative Svcs.*, 566 U.S. at 77 (holding method of treatment claims that included a step of administering known drugs described natural laws (*i.e.* "relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm") and, therefore, must be evaluated to determine whether the claimed process provided "additional features" that render the natural law a patentable invention); *Athena Diagnostics, Inc.*, 915 F.3d at 751 (holding that claims involving "both the discovery of a natural law and certain concrete steps to observe its operation" were directed to a natural law "because the claimed advance was only in the discovery of a natural law, and that the additional recited steps only apply conventional techniques to detect that natural law"); *see also* Tr. Vol. III at 117:17-20 (Plaintiffs conceding "the fact that human beings have these mutations is a natural phenomenon").

Plaintiffs in fact conceded unequivocally at the outset of trial that the crux of the asserted claims is the naturally occurring mutation pointing to the patient in need of the method Plaintiffs concede is prior art:

> So, to be clear, I want to be very clear about this, the first two parts of this, what to use for treatment and how to use it are prior art to the patents in this lawsuit. Let's make no mistake. They are prior art. The use of migalastat as a drug to treat people with responsive or amenable mutations is prior art. And how to dose them is prior art. And that, Your Honor, is where the '011 patent comes in. [The] '011 patent represents the work that was done to figure out how you should does those patients, which a very important part of this overall treatment. It's not the part that is the subject of the patents in this lawsuit. That's not the invention that we're looking at here.

Tr. Vol. I at 25:10-21 (Plaintiffs' Attorney Groombridge, making opening arguments).

Plaintiffs nonetheless contend that the asserted claims are not directed to a natural law because they recite the concrete step of administering a particular dosage of a drug, but these arguments have been soundly and correctly rejected by the Federal Circuit where the only distinction between the claimed method and the prior art method was the natural law itself. *See Athena Diagnostics, Inc.*, 915 F.3d at 751-52 (rejecting argument that claims at issue were directed to an innovative laboratory technique when the patentee could point to no "innovation other than its discovery of the natural law"); *INO Therapeutics LLC*, 782 Fed. App'x at 1006 (holding that claims directed to a multi-step method of treatment involving the use of a prior art drug were directed to a natural law because the only step in the claimed method distinguishing the claimed method from the prior art method was the step directed to the natural law). As in *Athena* and *INO*, the asserted claims are directed to methods Plaintiffs concede are, and the asserted patents themselves acknowledge as, prior art. The only distinction between the prior art methods and the asserted claims is the identification of naturally occurring Fabry mutations and, with respect to the '388 and '490 patents, an amenability determination based on (a) the patentees' observation of

migalastat's natural effect on the targeted mutation and (b) the patentees' own self-selected amenability criteria. The fact that the amenability assay employed by the patentees takes place in a laboratory utilizing manmade components is of no import here, where (1) the assay is not claimed or required to practice the claimed methods and (2) there is no evidence establishing the assay itself as innovative. *See Athena Diagnostics, Inc.*, 915 F.3d at 752 (rejecting argument use of a man-made substance in the method meant that it was not directed to a natural law when "the use of [the] man-made molecule . . . amounts to only a routine step in a conventional method for observing a natural law").

Therefore, Aurobindo respectfully submits the asserted claims are directed to the natural laws of Fabry mutation formation and migalastat amenability.

ii. The Asserted Claims Add Nothing to the Natural Laws Claimed.

Once it is determined that the claims are directed to unpatentable subject matter, the § 101 analysis requires the Court to determine whether the claimed inventions do anything to convert the unpatentable subject matter into a patentable invention. *Id.* at 753. In this case, they do not. With or without the amenability assessment factoring in, the asserted claims describe dosing methods that were well-understood and practiced by researchers in their field. Each of the asserted patents cites prior art dosing regimens identical to those claimed, including the Galafold product description dating back to 2016, and the '388 and '490 patents provide additional details regarding the prior art dosing regimen.

The claimed methods have only one step, administering 150 mg migalastat hydrochloride (or 123 mg of the freebase equivalent) every other day to the patient in need, and that step does not change depending upon the mutation or a finding of amenability. The finding of amenability according to the patentee's self-selected criteria tells practitioners nothing other than that the mutation met the patentees' self-selected criteria for amenability, but the trial record demonstrates

that others in the field used their own assays and set their own criteria for amenability, and there is no evidence of any universally adopted migalastat amenability criteria. *See*, *e.g.*, Tr. Vol. I at 132:22-134:17 (Dr. Medin addressing JTX-13, JTX-14 and noting the authors conducted their own HEK Assays using their own amenability criteria). An amenability determination cannot guarantee migalastat will work, and it does not tell even practitioners whether they ***should*** administer migalastat or instead pursue an alternative treatment for their patients. It also does not tell practitioners whether the mutation would meet more rigorous amenability standards. Thus, the amenability determinations embodied in the '388 and '490 patent claims do not tell practitioners how, when, or even to whom to administer migalastat safely and effectively.

Plaintiffs' argument that the mutation identification and amenability determinations inform decisions as to whether to prescribe migalastat ignores the above as well as the well-settled principle of law that the inventive concept at *Alice* step 2 cannot arise from unpatentable subject matter itself. *Athena Diagnostics, Inc.*, 915 F.3d at 754 ("The inventive concept necessary at step two cannot be furnished by the unpatentable law of nature itself" (corrections omitted)). Plaintiffs' argument that the limitations not directed to a natural law must be routine or conventional for the asserted claims to fail under *Alice* step 2 ignores § 101's plain language that an invention be "new," as well as the fact that Plaintiffs' previously patented the very same dosing regimen in the '011 patent, which regimen had been thoroughly studied and ultimately approved for marketing in Europe before the priority date for the patents in suit. It is, therefore, as routine and conventional as the precedent cited above requires. The cases on which Plaintiffs have relied are clearly distinguishable based on the facts set forth above.

Plaintiffs aim to protect their patent monopoly by adding amenable mutations to patent claims and their label as they evolve or are created and determined to be amenable contravenes 35

U.S.C. § 101 by effectively foreclosing the natural laws of Fabry mutation evolution and migalastat amenability. The asserted claims are directed to those laws, and they add no inventive step that would render those natural laws a patentable invention. Therefore, Aurobindo respectfully requests entry of judgment in Aurobindo's favor on its defense of lack of patentability under § 101.

B. The Asserted Patents Are Invalid Under 35 U.S.C. § 103.

The obviousness analysis under 35 U.S.C. § 103 is similar in this case to the § 101 analysis in the sense that Plaintiffs do not dispute that the dosing regimen claimed in the asserted patents is prior art. (*See*, *e.g.*, Tr. Vol. II at 136:16-22 (Dr. Hopkin conceding that dosing regimen was obvious).) Therefore, obviousness turns on the question of whether persons of ordinary skill in the art would have been motivated to combine the prior art teachings with at least a reasonable expectation of success of arriving at the claimed inventions (*i.e.* dosing directed to the specifically claimed Fabry mutations). With no shortage of prior art references to choose from, Aurobindo opted to proffer two prior art combinations at trial. The first combination points to a reference referred to at trial as "Lockhart" (DTX-26) and another referred to at trial as the "'319 publication" (JTX-11) The second combination points to the "Wu," (DTX-23) "Germain" (DTX-24) and "Benjamin 2016" (DTX-6) references. Both combinations disclose the claimed dosing regimen Plaintiffs concede is prior art, and both inform persons of ordinary skill in the art that any missense mutations would have about a 60% chance of being migalastat amenable and described and pointed to assays persons of ordinary skill in the art could perform to assess amenability with at least a reasonable likelihood of obtaining accurate results.

i. Qualifications of a POSA.

Although the parties proffered competing qualifications of persons of ordinary skill in the art ("POSA"), there is significant overlap between the two. Aurobindo nonetheless respectfully

submits that its proffered qualifications are clearer and consistent with the complexity of the art discussed in the asserted patents. Thus, Aurobindo submits that a POSA would have familiarity with metabolic disorders such as Fabry Disease and can include, for example, pharmaceutical chemists and physicians. They would be expected to have attained a high degree of education and would have earned either a Master's degree, Ph.D. or M.D., followed by several years of experience in the field. They would understand biochemical principles and have a high level of skill in the area of lysosomal diseases. The POSA would work as part of a collaborative team involved in drug formulation and clinical trial writing that would include multiple POSAs with expertise in various disciplines. And, they would be aware of the literature in the art, which is limited. (*See* Tr. Vol. I at 54:2-55:10 (Dr. Medin testifying regarding POSA qualifications).)

ii. Knowledge of a POSA Regarding Fabry Disease Before May 2017.

Prior to May 2017, a POSA would have been familiar with Fabry Disease, which was decoded in the 1970s by researcher Dr. Roscoe Brady. A POSA would have known that primary manifestations of Fabry Disease include a buildup of substrate in the vascular endothelium, which can lead to strokes or ischemia. A POSA would have known that the left ventricle of the Fabry patient's heart also becomes very thick and leads to myocardial issues, and the nephrons are also affected, leading to kidney issues. A POSA would have known that male Fabry patients typically die in their 40s and 50s. A POSA would have known that, oftentimes Fabry Disease is diagnosed by neuropathic pain or corneal whorls in the eye, something that can be seen by an optometrist or ophthalmologist. A POSA would have known that most often, Fabry patients are identified by neuropathic pain which starts to occur in their late teens or early 20s, and it can be so severe, the patients can become suicidal. (*See* Tr. Vol. I at 56:11-57:4 (Dr. Medin direct).)

A POSA would have been aware that protein mutations occur, giving rise to disease, but that some mutant proteins can be stabilized to function more naturally. A POSA would have been

familiar with the different types of mutations that give rise to disease, including missense mutations, which are mutations that occur on a position of the amino acid chain, and the amino acid has been changed from one to another, such as mutation I242F, which is a mutation on the 242 site where isoleucine has been changed to phenylene (*See* Tr. Vol. I at 57:22-59:22.)

A POSA would have been familiar with HEK assays, which are assays that utilize human embryonic kidney ("HEK") cells and which were developed in the 1970s by Dr. Frank Graham of McMaster University, who showed POSAs that they could put pieces of DNA in the HEK cells using plasmids that enter the HEK cells easily through a variety of methods with which a POSA would be familiar. POSAs would have known that you can then grow the plasmids for a long time. As of the 1970s, a POSA would have known that that you could use an artificial substrate called "four MUG," which the enzyme α-galactosidase A ("α-Gal A"), an assay protein, recognizes and cleans to make a fluorescent substrate that a POSA could read on a fluorometer and you can calculate observations against known standards to determine the level of enzyme activity in the cells being observed. Plasmids were put into the HEK cells in the 1970s. Mutant forms of enzymes were put into HEK cells in the early 1990s. A POSA would have known how to use a HEK assay to identify Fabry mutations, which can be taught to a graduate student in a very short time. HEK cells are the general workhorse cell lines for everyone in the field. (Tr. Vol. I at 61:5-63:7; 63:25-64:5.)

A POSA would have been familiar with the α-Gal A protein and its propensity for mutating from the early 1970s with the discovery of enzyme defects. Cardiac mutations were identified in α-Gal A in the 1980s and other mutations were identified in the 1990s. (Tr. Vol. I at 66:5-10.)

A POSA would have known that "GLP" refers to good laboratory practice, which was something that became standard with the U.S. Food & Drug Administration in 1978. GLP is

focused on quality assurance and quality control. It's concerned with laboratory processes, the conditions in which the processes are carried out, how they are planned, how they are performed, monitored, recorded, archived and reported. A POSA would know that GLP was not designed to establish relative merit or correctness. It is instead a quality assurance, quality control method to document experimental conduct. (Tr. Vol. I at 66:11-67:14.)

A POSA would have known of four treatments for Fabry Disease, including enzyme replacement therapy ("ERT"), substrate reduction therapy, molecular chaperone therapy and gene therapy, though only ERT and chaperone therapy currently have FDA approval, and prior to 2017, only ERT had been approved. (Tr. Vol. I at 73:5-74:8.)

A POSA would have known of migalastat, which was first isolated in 1988. (Tr. Vol. I at 74:18-75:1).

iii. The Asserted Claims are Invalid as Obvious over Wu, Germain, Benjamin and the Knowledge of a POSA.

The Wu reference (DTX-23) was published May 19, 2011, and is prior art to the asserted claims. Wu discusses migalastat using a variety of names and discloses that it is an amino sugar that serves as a chaperone in that it binds and stabilizes α-Gal A increasing total cellular levels. Wu mentions the development of a cell-based assay to identify mutant forms that are responsive to migalastat, which Wu discloses binds to the active site and chaperones α-Gal A into the right location. Wu discloses that migalastat increased α-Gal A activity in 49 of 81 mutant forms studied, approximately 60%. Wu discloses that missense mutations, which comprise about 60% of the Fabry mutations then known, are often identified as responsive to migalastat (*See* Tr. Vol. I at 76:1-78:4.)

The Germain reference (DTX-24) was published in 2012 and is prior art to the asserted claims. Germain discusses two Phase II clinical studies using a pharmacological chaperone.

Germain shows that you can demonstrate an increase in enzyme activity in HEK cells with the corresponding mutant form of the enzyme in the presence of migalastat. In other words, Germain shows migalastat's usefulness as a Fabry treatment and that six out of nine patients studied, each with missense mutations, were shown to be amenable to migalastat. Germain discloses migalastat being dosed in the studies at 150 mg every other day as being well-tolerated and increasing α-Gal A activity resulting in substrate reduction or Gb3 clearance. (*See* Tr. Vol. I at 78:19-80:22.)

The Benjamin 2016 reference (DTX-6) was published in 2016 and is prior art to the asserted claims. Benjamin 2016 discloses two studies evaluating 150 mg migalastat every other day as the dosing regimen. Benjamin 2016 discloses that study participants needed to have amenable mutations, and they were screened using a "preliminary" HEK-Assay. (*See* Tr. Vol. I at 80:23-82:14.) Benjamin 2016 further discloses the existence of the GLP-HEK Assay. (*See* Tr. Vol. II at 137:8-18 (Dr. Hopkin).)

A POSA would have been motivated to combine the teachings of the Wu, Germain and Benjamin 2016 references due to their overlapping subject matter, including that they are focused on migalastat as a pharmacological chaperone treatment for Fabry Disease, and Germain and Benjamin 2016 both point to the same dosing regimen, 150 mg of migalastat every other day. (*See* Tr. Vol. I at 95:24-96:10.) Moreover, a POSA would have drawn on their knowledge of HEK Assays, the migalastat amenability criteria disclosed in Wu and the disclosures establishing that about 60% of missense mutations, the same type of mutations claimed in the asserted claims, would be amenable to migalastat, which naturally would have motivated them to evaluate every Fabry patient with a missense mutation for amenability with at least a reasonable likelihood of identifying the mutation as amenable. (*See* Tr. Vol. II at 138:17-139:20; 144:22-147:5 (Dr. Hopkin testifying to his practice of ordering HEK Assay testing for mutations not on the Galafold product

list).) That is true, even if the specific mutation had been identified elsewhere as nonamenable given how HEK Assays are performed and the variability of amenability criteria. (*See* Tr. Vol. I at 88:14-107:12.) Therefore, a POSA would have combined the teachings in Wu, Germain and Benjamin 2016 with the POSA's knowledge with at least a reasonable expectation of arriving at the claimed inventions without undue experimentation.

Aurobindo respectfully submits the asserted claims are, therefore, invalid as obvious under 35 U.S.C. § 103 in view of Wu, Germain, Benjamin 2016 and the knowledge of a POSA.

iv. Asserted Claims Are Invalid as Obvious Over Lockhart, the '319 Publication and the Knowledge of a POSA.

The '319 publication (JTX-11) was published June 23, 2011, and is prior art to the asserted claims. The '319 publication discloses methods for determining the responsiveness to migalastat in a cell line, noting that at the time over 600 Fabry mutations had been reported, about 60% of which were missense mutations. It refers to migalastat as 1-deoxygalactonojirimycin or "DGJ," and discloses that missense mutations comprise the majority of mutations. (Tr. Vol. I at 82:21-85:19.)

The Lockhart publication (DTX-26) was published in 2015 and is prior art to the asserted claims. It discloses in multiple places the dosing regimen of 150 mg of DGJ hydrochloride, which is 123 mg of the free base migalastat, every other day (Tr. Vol. I at 85:20-87:12.)

A POSA would have been motivated to combine the teachings of the '319 publication and Lockhart publication due to their overlapping subject matter, including that they are focused on migalastat as a pharmacological chaperone treatment for Fabry Disease. (Tr. Vol. I at 96:11-16.) Moreover, a POSA would have drawn on their knowledge of HEK Assays, the migalastat amenability criteria disclosed in the '319 publication and the disclosures establishing that about 60% of missense mutations would be amenable to migalastat, which naturally would have

motivated a POSA to evaluate every Fabry patient with a missense mutation for amenability with at least a reasonable likelihood of identifying the mutation as amenable. (*See* Tr. Vol. II at 138:17-139:20; 144:22-147:5 (Dr. Hopkin testifying to his practice of ordering HEK Assay testing for mutations not on the Galafold product list).) That is true, even if the specific mutation had been identified elsewhere as nonamenable given how HEK Assays are performed and the variability of amenability criteria. (*See* Tr. Vol. I at 84:14-107:12.) Therefore, a POSA would have combined the teachings in Lockhart and the '319 publication with the POSA's knowledge with at least a reasonable expectation of arriving at the claimed inventions without undue experimentation.

Aurobindo respectfully submits the asserted claims are, therefore, invalid as obvious under 35 U.S.C. § 103 in view of the '319 publication, Lockhart and the knowledge of a POSA.

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